DIP #601

USMLE Step 2/3 Rapid Review Series 122

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- **Dr Mohammed Zaki**
https://chat.whatsapp.com/L6dShASc3f97cwHZgCD6Xo

Welcome

My name is Divine. This is episode 601 of the Divine Intervention Podcasts. And in today's podcast, we're going to be just talking about — or we're going to be doing — a rapid review series. So this is going to be a continuation of the rapid review series for the USMLE Step 2 CK and Step 3 exams, and this is going to be Series 122. Let's jump into it.

Iatrogenic Cushing Syndrome from Steroid Use

So what if they give you a question about a patient, and they tell you that this patient is a 52-year-old female, and that over the last 5 months, she has noticed that she has gained significant amounts of weight, and you're told that she has these purple linear lesions along her lower abdomen? And you're told that a year ago, this patient initially presented with a very significant headache — very significant headache — and at the time, inflammatory markers were elevated, and she was placed on appropriate pharmacotherapy. So they then ask, "What's the most likely etiology of this patient's symptoms?"

So I would really hope you're thinking about this person having some kind of iatrogenic Cushing syndrome. So what's the deal with that? Well, the deal with that is that this person had temporal arteritis — this person literally had giant cell arteritis.

And the thing is, when you have giant cell arteritis, typically it's going to present with a very significant headache. It doesn't just present with a headache — sometimes they can have eye pain, sometimes they may have jaw claudication. And remember, in addition to all those things, again, you have to go ahead and give them IV steroids very quickly — at least give them high-dose steroids. It may not even be IV, but give them high-dose steroids because that thing can cause blindness. That's the first thing you do. And then after you give them those high-dose steroids, down the line, you can then go ahead and do the temporal artery biopsy to confirm the diagnosis. You have a couple of weeks actually to do that temporal artery biopsy. So the first step in the management of any person with giant cell arteritis is to go ahead and give steroids.

So the thing is, this person has been on steroids for a long time. Remember, when a person is on corticosteroid therapy — I mean, when a person has giant cell arteritis, they have to be on corticosteroid therapy for a long time, for months often — because, again, you really want to protect their vision.

Now, the thing is, if you're taking steroids for that length of time, that can begin to cause a bunch of problems — like you can begin to cause Cushing syndrome. In fact, the most common cause of Cushing syndrome — the most common cause of cortisol excess — is exposure to iatrogenic steroids. OK? Exposure to iatrogenic steroids. That's something that's very high-yield for purposes of the USMLE exams.

Complications of Chronic Steroid Use

Now, what are some other derivatives? What are some other associations? What are some other integrations you can know with a person that is iatrogenically taking steroids?

Number one is that people that are going to be taking steroids for such prolonged periods of time — those people need to be placed on bisphosphonate therapy. OK? They need to be placed on what? On bisphosphonate therapy.

Why do they need to be placed on bisphosphonate therapy? Because corticosteroids activate osteoclasts. And when osteoclasts are activated, they can start chewing up your bone and cause osteoporosis. That's actually the mechanism behind corticosteroids causing osteoporosis. So these people should be on bisphosphonate therapy if they're going to be on steroid therapy for a long period of time, just to reduce their risk of having osteoporosis.

Another thing you should also keep in mind in a person that is chronically taking steroids is that it's also reasonable for those people to be on proton pump inhibitors, because again, corticosteroid therapy may trigger peptic ulcer disease. So it's helpful — if you're going to be on corticosteroids for a prolonged period of time — to also be on a proton pump inhibitor to stave off peptic ulcer disease.

Pneumocystis Pneumonia in Immunocompromised Non-HIV Patients

And then another thing to keep at the back of your mind is they can give you a question about a person that is on steroids, and you're told that for the last 3 to 4 days, the person has been having fevers, the person has been having shortness of breath, and then they tell you that you take a chest X-ray of the lungs and you find interstitial infiltrates. When you see that, I want you to think of *Pneumocystis jirovecii*. I want you to think of what? *Pneumocystis jirovecii*.

Many people ignore this, but the USMLEs these days — they like to give PCP pneumonia to people that are not necessarily HIV patients. For example, they can give PCP pneumonia to a person that is on chronic steroid therapy, because those things make you immunocompromised. They can give PCP pneumonia to a person that is taking a TNF inhibitor. For example, they can give it to a person that has SCID — where you have an adenosine deaminase deficiency or an interleukin-2 receptor defect. They can give it to many different kinds of people. They can give it to a post-transplant patient.

The thing is, when you think about these people, you realize that, oh yeah — these people are immunocompromised. But again, the schema that many people have built in their brains for *Pneumocystis jirovecii* pneumonia is people that have HIV. So again, they like to test these other schemas. That is one thing that I think many people lose sight of with the USMLE exams — this whole concept of new schemas. That's something I want you to keep in the back of your mind — same concept, but tested with a new schema.

So again, when people say, "Oh, when I took my exam, they tested a bunch of things I've never seen before," that's not exactly true. It's just not in the format that you're used to.

So let's go ahead and continue here.

SIADH and Drug-Induced Hyponatremia

Okay, so what if they give you a question about a 44-year-old male? You're told that he has a past history of diabetes. And you're told that over the last 3 weeks, this person has been altered. This person has been altered. This person has not been doing very well. And you're told that, again, 3 months ago, he did come in for diabetes management. He was already on metformin, but his A1C was not well controlled.

But now he's been altered for the last 3 weeks. And they show you some labs. They show you that his A1C 3 months ago was 7.0. His A1C now is like 6.2, so things are getting better. And then they show you that his serum sodium is like 151 — so it's kind of high. And then they show you that—his serum sodium is 127, and his urine osmolarity is very, very high. You're told that, oh, his urine osmolarity is like 800 or something like that.

When you see something like that, what should you be thinking about? I would really hope you're thinking about SIADH.

Let me explain.

First things first: we know that SIADH is associated with a low serum osmolarity and a high urine osmolarity. And why is that? The thing is, when you have high levels of ADH, it's going to cause you to suck up a lot of free water from your urine. As you suck up all that free water from your urine, it's going to be returned back to the serum. That is going to lower your serum sodium concentration. So you're going to have hyponatremia. That's probably why this guy has altered mental status.

But at the same time, all that water you're sucking up from your urine is going to make your urine very, very concentrated. So you're going to have concentrated urine. You're going to have a high urine osmolarity.

Because the thing is, if you really think about it, the normal response — if you have a low serum osmolarity — is potentially to also have a low urine osmolarity. Because when your serum osmolarity is that low, then you want to let go of as much fluid as possible in your kidneys so that you can restore that serum osmolarity.

But you're not able to do that when you have SIADH, because you have just tons and tons of ADH being produced, and that's causing you to get into trouble.

So what diabetes drug must this person have been placed on to cause SIADH?

This is something you don't find in many resources, but it's actually very, very high-yield to know for your exams. And that's **chlorpropamide**.

I'm going to spell it: C-H-L-O-R-P-R-O-P-A-M-I-D-E. Chlorpropamide is a sulfonylurea.

Chlorpropamide has a very, very strong association with SIADH.

Because the thing is, the USMLEs — they're not stupid. They know that many of you that have the job description "medical student" or "USMLE exam taker" — you've memorized the classic names of sulfonylureas. I'm sure they know that you guys are familiar with glyburide and glipizide and glimepiride.

So it behooves them to test something that is a sulfonylurea — it's exactly like a sulfonylurea — but it doesn't sound like many of the sulfonylureas. It starts with a "C" instead of a "G": chlorpropamide.

Now, please don't forget the other causes of SIADH.

Don't forget SSRIs. SSRIs are one of the most common — if not the most common — drug causes of SIADH.

And remember, you can also see SIADH with **carbamazepine**. So they can give you a question about a person that is being treated for **trigeminal neuralgia**, and the person develops SIADH as a result.

And then, don't forget — if you see SIADH in a long-term smoker, you should think about **small cell lung cancer**. They can have SIADH as a **paraneoplastic** phenomenon under those circumstances. So that's something you really want to keep at the back of your mind for exams.

So make sure you know about SIADH.

And honestly, if we're being honest with ourselves, pretty much any **brain problem** can cause SIADH. Pretty much any **pulmonary problem** can cause SIADH. You can even have **pneumonia**, and that can cause SIADH. You can even have **meningitis**, and have SIADH.

So please keep that at the back of your mind as you prepare for exams.

DiGeorge Syndrome: Hypocalcemia & Absent Thymus

Now, what if they give you a question about a **newborn**? You're told that this is a **3-hour-old newborn**, and you're told that this child has been having **tetanic contractions**. And they give you a newborn chest X-ray, and you notice that the chest X-ray shows a **normal cardiac silhouette**, and you notice that this newborn has — they use the term — **reduced supramediastinal radiodensity**.

What's your diagnosis for this child?

I really hope you're saying: "Divine, this is **DiGeorge syndrome**."
And you might feel like, "Wait — DiGeorge syndrome?"
Yes! This is absolutely, positively **DiGeorge syndrome**. Absolutely, positively DiGeorge syndrome.

So first things first — why does this child have tetanic contractions?

This child has tetanic contractions because the child has **hypocalcemia**. Because remember, in DiGeorge syndrome, the **pathophysiology** involves you not having your **3rd and 4th pharyngeal pouches**.

So because you lack pharyngeal pouches number 3 and 4, you have **no thymus** — so you're going to struggle with **T cells**. You're going to struggle with a lot of **viral and fungal infections**. But you also have **no parathyroids**, so you're not making **PTH**. Because you're not making PTH, you cannot raise your serum calcium level, so you're going to have **hypocalcemia**.

That hypocalcemia can cause **seizures**. It can cause **tetany**.

Remember, when you have hypocalcemia, you can have things like the **Chvostek sign** — where you tap the cheek and you see **facial muscle spasms** — or you can have the **Trousseau sign**, where you try to take a blood pressure, you tighten a blood pressure cuff on a person's arm, and they have **carpopedal spasms**.

So what do I mean in this vignette when I talked about the reduced supramediastinal radiodensity?

I'm just basically saying that **there is no thymus**.

Again, see — I could have made your lives easier and said "no thymus, no thymus." But the thing is, the USMLEs — again, they are not stupid. You see me — I say this all the time — but these people that write these exams, they are truly not stupid. Because they recognize that all of you have memorized, "Oh, no thymus in DiGeorge syndrome." They know that it's in every resource known to mankind that is geared to prepare you for the USMLEs.

So what do they do? They just take what you know — and express it in different terms.

That's what I do with many of my podcasts. That's what I do with many of my review courses. Because again, if you're not familiar with these other terms for stuff, then you're not truly preparing yourself well for the exams. That's just the truth.

So the term **reduced supramediastinal radiodensity** is just another fancy-schmancy way of saying that this person **does not have a thymus**.

If you don't have a thymus, well, you're not going to have T cells. And you're going to struggle. So that's very high-yield to know for purposes of your exams.

Many of you are familiar with the **absent sail sign**.

Remember, if you see the thymus, you're going to see a **sail sign**. Make sure you can identify a thymus on a newborn chest X-ray. If you don't see it, that's an **absent sail sign**.

There are some very classic causes of that for the USMLEs.

DiGeorge is a very classic one.

Another classic one you may see on your exams is **SCID** — Severe Combined Immunodeficiency.

Remember, there are two causes of SCID. The **most common cause** is the **X-linked recessive version**, where you have an **interleukin-2 receptor gamma chain defect**. So because you have that interleukin-2 receptor defect, you're not able to properly stimulate your B and your T cells. So you have a **combined immunodeficiency**.

But also, at the same time, if a person has an **adenosine deaminase (ADA) deficiency** — that's more of an **autosomal recessive** SCID — you're going to have **premature lymphocyte apoptosis**. That's also going to cause you to have SCID.

And again, just by the way, since we talked about DiGeorge syndrome — don't forget: **chromosome 22q11 deletion**.

You're going to make the diagnosis of DiGeorge by doing **fluorescence in situ hybridization — FISH**.

Again, I know many of you preparing for Step 2, Step 3 would never imagine that the words "FISH" or "fluorescence in situ hybridization" would be on your exams — huh. But I kid you not — it can be.

Literally, what FISH does is it detects that **chromosome 22q11 deletion**.

Subperiosteal Resorption and Primary Hyperparathyroidism

Now what if they give you a question about a **50-year-old female**, and you're told that this 50-year-old female has been having a lot of **hand pain** for the last 3 months?

And then they tell you that they get a **radiograph** of this person's hand, and they notice **subperiosteal resorption** — they use that term — **subperiosteal resorption**, along the **lateral aspects**, especially of the **middle phalanges**.

When you see something like this on your exams, what should you be thinking about?

I would really, really hope you're thinking about what?
Primary hyperparathyroidism. I would really hope you're thinking about what?
Primary hyperparathyroidism.

So I know you may be like, "OK Divine, what exactly are you talking about?"

Well, the thing is, again — the USMLEs, they know that many of you already know what's in the classic resources about primary hyperparathyroidism. They know that if you have primary hyperparathyroidism, that's the **most common cause of hypercalcemia in the outpatient setting**.

Remember, **primary hyperparathyroidism** is the most common cause of **hypercalcemia in the outpatient setting**.
But the most common cause of **hypercalcemia in the inpatient setting** is going to be **malignancy**.

And they know that when a person has primary hyperparathyroidism, they're going to be making lots of **PTH**.
And one of the jobs of PTH is to **raise your serum calcium levels**. So the **serum calcium is going to be high**.

Well, what else does PTH do to phosphate?
Think of **PTH as the phosphate-trashing hormone** — the **phosphate-trashing hormone**.
So because PTH is a phosphate-trashing hormone, it's going to trash your phosphate through your kidneys — so your **phosphate is going to go down**. You're going to have **low phosphate**.

But one thing you want to keep in mind is this whole concept of **urinary calcium**.

Because your **serum calcium is high**, your body is going to be like, "Oh no — I don't like having this high serum calcium," so it's going to **dump some of that calcium in the urine**. So you're going to have **high urinary calcium**.

This is **very high-yield** to know for your exams. When a person has primary hyperparathyroidism, they can have:

- High **serum calcium**
- High **urinary calcium**
- Low **serum phosphate**

Because again, they're literally dumping phosphate in the urine.

Now, the thing that people do not think about with primary hyperparathyroidism is that **PTH is stimulating your osteoclasts**.

Although remember — **PTH does not directly stimulate osteoclasts**. It stimulates your **osteoblasts first**, because the **PTH receptor is actually on osteoblasts**.

It stimulates your osteoblasts first, and then your osteoblasts release something called **RANK ligand**, which then binds to the **RANK receptor** that we find on the surfaces of osteoclasts. And then that's going to stimulate those osteoclasts.

As your osteoclasts are resorbing your bone, you're going to see that **subperiosteal resorption**.

I'm telling you this — you may think, "Why is Divine mentioning this term over and over again?"

It's a term that, for whatever bizarre reason, **doesn't pop up in many resources**, but for whatever bizarre reason, it **pops up a lot on the USMLE exams**:

Subperiosteal resorption — just below the periosteum of the bone.

If you literally see those words on your exams — **subperiosteal resorption**, especially along the **lateral aspects of your middle phalanges** of the hands — think about a person who has **primary hyperparathyroidism**.

Don't forget that the **most common cause of primary hyperparathyroidism** is a **parathyroid adenoma**.

The **second most common cause** of primary hyperparathyroidism is **parathyroid hyperplasia**, where you have just an increase in the number of cells in your parathyroid gland.

So remember:

- **Hyperplasia** = increase in **cell number**
- **Hypertrophy** = increase in **cell size**

Please be careful about that.

So again:

- Most common cause of primary hyperparathyroidism = **parathyroid adenoma**
- Second most common = **parathyroid hyperplasia**

And don't forget, there are **other things** that can cause primary hyperparathyroidism on your exams — like the **MEN syndromes**, especially **MEN 1** (that's autosomal dominant, **MENIN** gene mutation) and **MEN 2A** (also autosomal dominant, but that's from a **RET** mutation).

Remember:

- **MEN 1**: Parathyroid adenomas + pituitary + pancreatic tumors
- **MEN 2A**: Medullary thyroid cancer + pheochromocytoma + parathyroid hyperplasia
- **MEN 2B**: No parathyroid involvement

So **MEN 2B** does **not** have primary hyperparathyroidism as a feature.

Primary Hyperparathyroidism vs Familial Hypocalciuric Hypercalcemia (FHH)

And one last thing I want to say — and then we'll kind of wrap this podcast up — again, this is a rapid review series, so I'm just hitting a lot of stuff hard.

If you remember, for **primary hyperparathyroidism**, I said you're going to have:

- **High serum calcium**
- **High urinary calcium**
- **Low serum phosphate**

Well, here's where you want to be careful:

There is **another disorder** that sometimes our friends at the NBME want you to **compare side-by-side** with primary hyperparathyroidism. And that's:

Familial hypocalciuric hypercalcemia — **FHH**

This is a disorder where you have a **mutation in the calcium-sensing receptor** — a mutation in the **CaSR**.

So what does the calcium-sensing receptor do?

It does two things:

1. In your **serum**, it tells your parathyroid gland,
   "Hey, my calcium is too high."
   So whenever you have high serum calcium, it tells your parathyroid glands:
   "Okay guys, calcium is high — let's stop PTH production."

2. In the **kidneys**, it tells your kidneys:
   "Hey, serum calcium is high — stop reabsorbing calcium."
   So the normal response is to dump excess calcium in the urine.

But if you have a mutation in this receptor, even if your **serum calcium is high**, it's **not able to signal** to the parathyroid glands to **stop making PTH**.

So those glands are going to **keep making PTH**, and you're going to **keep raising your serum calcium levels** — so you're going to have **hypercalcemia**.

Now, in the kidneys, the **mutated CaSR** also fails to signal:
"Hey, calcium is high — stop pulling calcium back in."
So your kidneys **keep reabsorbing calcium**, and as a result, your **urinary calcium is very low**.

So people with **familial hypocalciuric hypercalcemia (FHH)** will have:

- **High PTH**
- **High serum calcium**
- **Low urinary calcium**

Much unlike the people we see that have **primary hyperparathyroidism**, who have:

- **High PTH**
- **High serum calcium**
- **High urinary calcium**

That's a very nice way to **differentiate** the two conditions.

And remember — when people have FHH, **you don't have to treat them**.